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| EXAMINER | |
|---|---|
| ZHENG, LI | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/539,891 | NAPIER ET AL. | |
| | Examiner | Art Unit | |
| | Li Zheng | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *04 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *10-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 June 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6172005/9262005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-25 are pending.

### *Election/Restrictions*

2. Applicant's election with traverse of Group II group (a), claims 1-9, SEQ ID NO: 1, 3 and 5, a residue of the general formula II as R1, unsaturated C2-C24-alkylcarbonyl as R2 and R3, n being 3, m being 4, P being 3 and the plant being rapeseed in the reply filed on 5/04/2007 is acknowledged.

Applicants contend that all the species have the same property as lipids and share common structure as depicted in formula I and therefore all requirements for proper Markush practice are satisfied (response, page 4).

The office contends that the formula I contains unmanageable numbers of species, many of which have distinct structures and thus require search for different fields. The species election is proper. See MPEP § 803.02.

Claims 10-25 are withdrawn.

Claims 1-9 including SEQ ID NO: 1, 3 and 5 are examined on the merits.

The restriction is still deemed proper and is made FINAL.

### *Specification*

3. Figure 3 is objected to because the label for one of the compounds is missing.

### *Claim Objections*

4. Claim 1 is objected to for reciting "a one third nucleic acid sequence". The recitation "a" should be deleted.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the phrase "if necessary" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. The metes and bounds are not clear. See MPEP § 2173.05(d).

***Written Description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method using a nucleotide sequence which encodes any delta-9-elongase, any delta-8-desaturase or any delta-5-desaturase, or peptides having at least 50% sequence identity to the amino acid sequence set forth in SEQ ID NO: 1, 3 and 5.

The specification only teaches SEQ ID NO: 3 as delta delta-9-elongase (specification, page 43, lines 19-22), SEQ ID NO: 1 as delta-8-desaturase (specification, page 42) and SEQ ID NO: 5 as delta-5-desaturase (specification, page 46, lines 15-30).

The Applicants do not identify essential regions of the protein of delta-9-elongase, delta-8-desaturase, delta-5-desaturase or SEQ ID NO: 1, 3 or 5, nor do Applicants describe any nucleotide sequence encoding a polypeptide

sequence that has at least 50% identity to SEQ ID NO: 1, 3, or 5, except for SEQ ID NO: 1, 3 or 5 itself.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. The court goes on to say, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of polynucleotide sequences encoding the protein encoded by SEQ ID NO: 1, 3 or 5 falling within the scope of the claimed genus of polynucleotides which encode polypeptides at least 50% identical to SEQ ID NO: 1, 3 or 5. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of polynucleotides. In fact, Sayanova et al. (2006, FEBS Letters 580:1946-1952) teach that enzymatic activities associated with the alternative delta-9-

elongase/delta-8-desaturase are only reported only in several unicellular organisms (page 1946, 2nd paragraph of the right column). The sequence information related to those enzymes is quite limited at the time of the invention. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for the protein of delta-9-elongase, delta-8-desaturase, or SEQ ID NO: 1, 3, 5, it remains unclear what features identify a (give the species) protein of SEQ ID NO: 1, 3, or 5. Since said genus has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

***Enablement***

7. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for accumulate C20 polyunsaturated fatty acids in transgenic Arabidopsis plant expressing SEQ ID NO: 1 and 3, does not reasonably provide enablement for any transgenic organism expressing any delta-9-elongase and any delta-8-desaturase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400

(Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are drawn to a method for the production of compounds as depicted in formula I of claim 1 in transgenic organism with a content of 1% by weigh of said compound-referred to the total lipid content by transgenically expressing a delta-9-elongase gene and a delta-8-desaturase gene in host cell.

The specification teaches isolation of SEQ ID NO: 3 as delta delta-9-elongase from Isochrysis (specification, page 43, lines 19-22), SEQ ID NO: 1 as delta-8-desaturase from Euglena (specification, page 42) and SEQ ID NO: 5 as delta-5-desaturase from Phaeodactylum (specification, page 46, lines 15-30). The specification further teaches transforming Arabidopsis and oilseed rape plant with SEQ ID NO: 3, SEQ ID NO: 3 and 1, or SEQ ID NO: 1, 3 and 5 (specification, page 46, line 10 to page 48, line 23). The GC profiles of Arabidopsis leaf fatty acid methyl esters from those transgenic lines were obtained (page 50, Table 1). The specification also teaches that in the stably transformed transgenic lines of oilseed rape expressing delta-8-desaturase, there

is an increased content of double bonds at the delta-8-position by comparison with untransformed control plants (page 48, lines 13-20). The specification further proposes to produce transgenic flax plants in a similar way (page 48, lines 25-30).

The specification fails to provide guidance on how to practice the invention for any transgenic organism. The specification only teaches working examples in Arabidopsis (with data) and oilseed rape plant (without data). The specification failed to provide guidance to practice the invention in other organisms including mammalian hosts and microorganisms. For example, there is no evidence that the genes function in a prokaryotic host, such as a bacterium. Sayanova et al. also teach that the status of C20 delata-8-desaturase activity in mammalian tissues remained unresolved (page 1946, 2nd paragraph of right column). Even for plant hosts, the specification only provide data for Arabidopsis, there is no evidence that the transgenic genes would function at least as efficiently in other plant to achieve the a content of 1% or 5% by weigh of said compound-referred to the total lipid content

The specification also fails to provide guidance in terms of how to make modifications to the SEQ ID NO: 1, 3, or 5 to generate the claimed genus of variants that retain their enzymatic activities. As discussed above, the specification fails to provide conserved structure that are essential for the functions of SEQ ID NO: 1, 3 or 5.

Falcon-Perez JM et al. (1999, *J Biol Chem.* 274:23584-90) teach that when twenty-two single amino acid substitutions or deletions were introduced

into the nucleotide binding domains, the proposed regulatory domain, and the fourth cytoplasmic loop of the yeast cadmium factor (Ycf1p) vacuolar protein by site-directed mutagenesis, two conserved amino acid residues, Glu (709) and Asp (821), were found to be unnecessary for Ycf1p biogenesis and function.

The state of art also teaches that making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al. (1988, Mol. Cell. Biol. 8:1247-1252) teach that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins would have at least 95% identity to the original protein.

Guo et al. (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2).

Therefore, the instant specification fails to provide guidance for which amino acids of SEQ ID NO: 1, 3 or 5 can be altered, the type of alteration, and which amino acids must not be changed, to maintain enzymatic activities of the encoded proteins. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

Still further, the working example in the specification only shows the data for the content of C20 polyunsaturated fatty acids such as the ones listed in table 1, it does not provide any evidence that other compounds in the formula I of claim 1 are produced by the instant method. There is no evidence that the transgenically expressed enzymes would produce such unmanageable number of compounds as depicted in claim 1.

Without further guidance, undue experimentation would be required for a person skilled in the art to practice the invention using nucleic acids encoding a polypeptide having at least 50% identity with the polypeptide of SEQ ID NO: 1, 3 or 5, or to produce claimed compounds at claimed content levels. See *Genentech Inc. v. Novo Nordisk,* A/S (CA FC) 42 USPQ2d 1001 (Fed. Cir. 1997), which teaches that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Therefore, given the claim breadth, lack of further guidance and additional working example, unpredictability of the art, undue experimentation would be required for a person skilled in the art to practice the invention in full scope.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mukerji et al. (2004, U.S. Patent No. 6,677,145) in view of Browse et al. (2004, U.S. Patent No. 6,825,017).

The claims are drawn to a method for the production of compounds as depicted in formula I of claim 1 in transgenic organism with a content of 1% by weigh of said compound-referred to the total lipid content by transgenically expressing a delta-9-elongase gene and a delta-8-desaturase gene in host cell, or wherein the transgenic host is a oil producing plant; or wherein the compound are isolated in form of their oils, lipids of free fatty acid;

Mukerji et al. teach an alternative delta-8-desaturase pathway through which 18:3n-3 can be converted to 20:4n-3 by elongase and delta-8-desaturase (Figure 1). Mukerji et al. further teach that transgenically expressing elongase can increase C20:3n-3 production by at least 2.3% (Figure 57, C, pRAE-84).

Mukerji et al. et al. does not teach transgenically expressing delta-8-desaturase.

Browse et al. teach a transgenic plant cell expressing delta-8-desaturase and delta-5-desaturase (claims 21-26). Browse et al. also teach delta-8-desaturase and delta-5-desaturasecan be used individually or in conjunction with one another to produce polyunsaturated fatty acid (column 3, lines 24-27).

Given the recognition of those of ordinary skill in the art of the value of increasing polyunsaturated fatty acid, it would have been obvious for a person with ordinary skill in the art to transgenically express both delta-9-elongase gene of Mukerji et al. and delta-8-desaturase and delta-5-desaturase of Browse et al., resulting in the instant invention. One skilled in the art would have been motivated to do so given the teaching of Mukerji et al. that polyunsaturated fatty acid can be produced by an alternative delta-8-desaturase pathway and the teachings of both Mukerji et al. and Browse et al. that expressing delta-9-elongase and delta-8-desaturase individually could produce more polyunsaturated fatty acid. Expressing both of genes would be expected to produce more polyunsaturated fatty acid. The other features in the instant claims are obviously exhibited by the combined teaching of the references.

Thus the claimed invention would have been *prima facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Li Zheng whose telephone number is 571-272-8031. The examiner can normally be reached on Monday through Friday 9:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571-272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ELIZABETH MCELWAIN
PRIMARY EXAMINER